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Food and Drug Administration
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Rockville, MD 20852

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Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices; Docket No. 98N-0222

To Whom It May Concern:

The patient, health and consumer organizations submitting these comments urge the Food and Drug Administration (FDA) to enact strong regulations governing the dissemination of information related to unapproved and new uses of marketed drugs, biologics and devices. It is imperative that the FDA take every step to ensure that all materials circulated meet the highest scientific standards possible and are presented in a context that clearly informs recipients that the products have not been proven safe and effective for the indication being promoted.

In passing Sec. 401 of the Food and Drug Administration Modernization Act (FDAMA), Congress created an exception to one of the most fundamental tenets in the nation's regulatory system -- that new products be proven safe and effective prior to their marketing by the manufacturer -- and thus moved the FDA into uncharted territory. The dangers of this provision are clear. New uses often apply to a much larger and different patient population and often for a significantly different use than the approved indication. Congress is now allowing manufacturers to actively disseminate information about such new uses without first conducting the research to prove that these new uses are safe and effective. As a result, millions of Americans will be using products whose safety and effectiveness have not been established.

In creating this exception, Congress did not intend to abdicate all safeguards to prevent harm to patients as a result of using a product for an unproven use. Indeed, safeguards are more important when safety and effectiveness have not been established. Public involvement at every stage of the process will help to ensure that such safeguards are used to the full extent possible. The resource-strapped FDA must incorporate appropriate public access in order sufficiently monitor the actions of the manufacturers and to help prevent to manufacturers from abusing the privileges granted to them under this section and to help assure that patients and their providers are able to make more fully informed decisions.

Public Information

Manufacturer's Submissions to the FDA

Sec. 401 of the statute, and the ensuing regulations, require manufacturers to submit a number of important documents to the FDA prior to dissemination of information and after dissemination commences. Prior to dissemination, the manufacturer must submit, in addition to the information to be disseminated: all other clinical information that it has relating to the safety or

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effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use and a summary of such information, and the search strategy used for developing the required bibliography.

In relation to the required submission for the new use, the manufacturer must provide:

*a supplemental application for the new use;

*a certification that an application will be submitted within six months of dissemination;

*a proposed protocol and schedule for conducting the trials necessary for a supplemental and certification that such trials will be completed in 36 months; or

*a request for an exemption from the supplemental application requirements.

Specifically, when requesting an exemption, the manufacturer is required to explain why an exemption is sought along with materials demonstrating that it would be economically prohibitive or unethical to conduct the studies needed for submission of a supplemental application.

Once dissemination has begun, the manufacturer must submit any new information that becomes available about the new use. Every six months, it is required to submit lists of the titles of the articles and publications that have been circulated in the previous six-month period and the individuals or categories that have received the materials. Manufacturers that have committed to conducting studies necessary for a supplemental application must also submit status reports on those studies. They may also submit a request for an extension of the 36 months period for up to 24 additional months and, if granted, must submit a new time frame for the completion of studies.

The Public's Right to Know

Clearly, this information is of vital importance to the health of the public. Both the individuals and their physicians who use a product for the new use and those who can provide appropriate balancing information and monitor the progression of clinical investigations need access to the information submitted by the manufacturer. Patients and health care providers have a right to know all additional safety and effectiveness data available so that they can be fully informed prior to using a drug for a promoted off-label use. The public has a right to know what studies are being conducted to prove safety and effectiveness and the status of those trials. Thus, it is critical that all the information submitted in Sec. 551, 552, 553, and 554 of the Food, Drug, and Cosmetic Act, as outlined above, be available to the public.

The Role of the Public in Providing Balancing Information
Given the FDA's extremely limited resources and the substantial new burden that these regulations place on the FDA, the public clearly has a pivotal role to play in monitoring the dissemination of information about unapproved uses.

Many patients, their families and health care providers have an in-depth knowledge of the published studies related to a specific disease or condition, which the FDA itself may not have. Given the value of this resource and the important role that it can play in facilitating distribution of the most balanced information possible, the FDA, upon receiving a submission from the manufacturer [99.201], should publish immediately in the Federal Register the citation for the article and the bibliography to be disseminated and solicit additional published information that might be appropriate for distribution or inclusion in the bibliography. Just as there is an opportunity for public comment prior to the marketing approval of new products or supplemental applications, so too should the public be given the opportunity to comment prior to the granting of approval for dissemination of information on an off-label use.

The Role of the Public in Monitoring Trials
Congress placed great weight on the diligent conduct and timely completion of the trials necessary for a supplemental application in allowing the dissemination of information on unlabeled uses. Again, given the FDA's limited resources and expanding responsibilities, the public has an important role to play in monitoring the timely conduct and completion of these trials. Public monitoring is all the more necessary given the significant portion of required post-marketing studies that have not been completed in the past and the FDA's poor track record of monitoring their status. Thus, all information submitted under Sec. 554 of the FDCA must be public so that the public can fulfill its important role in monitoring the progress of these studies to facilitate their timely completion.

The Public's Right to New Information
If members of the public will be prescribed a product for an unproven use, which is the manufacturer's goal in disseminating that information, then they and their health care providers have a right to all known information about the safety and effectiveness of that use. By definition, the safety and effectiveness of the use have not been established and, thus, patients are essentially using the product in an uncontrolled experimental setting. Therefore, patients and their practitioners must have access to all data, including but not limited to trial designs, possible adverse events contemplated by the protocol, adverse events as they arise over time, and any other safety or effectiveness information that would facilitate the most appropriate care. For these reasons, when the FDA approves the manufacturer's request to disseminate the information, the public should then have access to any existing or future safety and effectiveness data. To keep such information from the public, while allowing that use to be actively promoted by the manufacturer, would be unethical and counter to the best interests of the public's health.

The Public's Right to Participate in the Exemption Process

The process of deciding whether or not to grant an exemption from filing a supplemental application on economic or ethical grounds must be conducted on the record and include meaningful public input. The potential harm that may result from the FDA's decisions in such circumstances is of a magnitude to cause substantial concern. By granting such an exemption, the FDA will be giving the manufacturer the right to promote a use of a product indefinitely without ever establishing its safety and effectiveness. Under such circumstances there is the potential for harm to the public. Therefore, prior to granting any exemption, the FDA should hold a meeting of the appropriate advisory committee(s), so that the public has the opportunity to review and comment upon the request. Granting exemptions under any circumstances is, given the great potential for harm to the public, itself an ethical decision (e.g. deciding the economic constraints outweigh the possible risks of never establishing a product's safety and effectiveness is an ethical decision) that requires the most thorough and rigorous review. The idea that ethical decisions with such a tremendous impact on the public health might be made behind closed doors and without the involvement of the public who will use the products is inconceivable.

As the FDA correctly stated in the proposed regulations, Congress intended for the granting of any exemption to be extremely rare, so the inclusion of a an advisory committee meeting in the process should not create an undue burden on the FDA.

Claims of Confidentiality of Information are Baseless

Some may argue that information submitted to the agency under Sec. 551, 552, 553, and 554 should be accorded the level of confidentiality given to information in new drug applications. Such arguments are baseless, inappropriate and contradictory. Arguments that supporting materials should be kept confidential are not applicable given the fact that the manufacturer is proactively circulating information in an attempt to get more doctors to prescribe their product for a given use. To prohibit the public release of all supporting data prevents practitioners and their patients from making decisions based on the full range of available information, which would be especially ironic given that Sec. 401 of FDAMA was supposedly enacted so that doctors and patients would have better access to information.

It is implausible to suggest that commercial considerations require such data be kept from the public. By circulating the article, the manufacturer has declared publicly that they have or will conduct clinical investigations on this specific use with the aim of getting that use added to the approved labeling. Competitors will undoubtedly know about a drug that is already approved, in use, studied sufficiently to produce journal articles and reference works on new uses, and the subject of materials distributed to practitioners and others to highlight other uses.

There are no convincing arguments for confidentiality when compared to the compelling public need for such information. Unlike other situations in which patients take a drug whose safety and effectiveness have not been established (i.e., clinical trials of new drugs), these patients are taking such drugs in an uncontrolled environment under the supervision of providers who will often not be expert in the drug or its potential effects. Such providers and such patients should

have all possible information to help facilitate the safe and effective use of these drugs that have not gone through the usual demonstration of safety and effectiveness.

Criteria for information to be disseminated

The statute states that reprints and reference publications be "about a clinical investigation... which would be considered to be scientifically sound by [qualified] experts." The FDA's draft regulations outlining the criteria for acceptable reprints and reference publications are necessary to comply with the clear meaning of the statute. Requirements that the reprint or reference publication contain comprehensive trial report information including the study's design, conduct, data, analyses, and conclusions [99.101 (b)(1)] are essential for determining the scientific soundness of the clinical investigation that is the subject of the article or publication. This portion of the proposed rule is a clear and reasonable definition of "scientifically sound" that gives guidance to manufacturers as to the type of studies that will be acceptable.

Disclosure statements

The statute requires that the manufacturer include with the information that is to be disseminated a "prominently displayed" statement disclosing a list of important information [99.103]. The FDA's proposed regulations outline what criteria it will use in determining whether the statement is "prominently displayed" in an effort to make the implementation of the statutory requirement consistent and simply reiterates the list of information that must be included in the disclaimer as required by the statute. Such guidance is necessary to clarify what is meant by "prominently displayed" so there is no confusion about what is required of manufacturers. The "prominently displayed" statement in no way interferes with the manufacturer's ability to disseminate information.

Definition of new use

The proposed regulations logically state that any use that is not included in the approved labeling of an approved drug or in the statement of intended use for a cleared device is considered a new use. This regulatory definition of "new use" is consistent with the statute, which applies to uses "not described in the approved labeling of a drug or device." The FDA has correctly interpreted this to mean any use that would require a supplemental application in order to be included in the label. This regulatory definition of "new use" is appropriate and must be preserved in the final regulations.

Record Keeping

One important safeguard in the legislation requires a manufacturer to maintain records of the recipients of the disseminated materials so that the manufacturer can notify the recipients if it is later determined that the new use is ineffective or poses a significant risk to public health. The proposed regulations permit the manufacturers to decide whether to keep records that identify the individual recipients of the information or the category of recipients. In order to ensure that all the people who have seen and relied on the disseminated information will learn of the risks associated with the promoted use, the FDA should use the discretion given it by Congress to require the manufacturer to maintain specific records of the individual recipients of the

information in all cases. A categorical list of recipients is not sufficient to comply with the safeguard outlined in the statute. Complete and thorough corrective actions appropriate for the protection of public health will occur only if the manufacturer keeps specific records identifying the individual recipients of the disseminated information and then notifies those individuals directly.

In addition, requiring manufacturers to maintain lists of individual recipients will help meet another safeguard of the legislation--that the information be disseminated only to individuals in select categories. By requiring companies to maintain lists of recipients, the FDA will help to assure that companies distribute materials only to the appropriate individuals by using tightly controlled mechanisms, such as direct mailings, that will facilitate maintaining an accurate list of recipients.

Conclusion

As the FDA moves forward with the implementation of the final regulations, it is crucial that every possible safeguard be put into place in order to protect the health of the American public. The FDA must take every step possible to fulfill its mission to protecting the public health in the face of regulations that will put into place a mechanism allowing the promotion of new uses that have not been proven safe and effective.

These comments are being submitted on behalf of the Patients' Coalition members listed below:

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Center for Medical Consumers
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Committee for Children
2112 New Hampshire Avenue, NW, Suite 1008
Washington, DC 20009

Consumer Federation of America
1424 16th Street, NW
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Epilepsy Foundation
4351 Garden City Drive
Landover, MD 20785

Gay Mens' Health Crisis
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Guillain-Barre Syndrome Foundation International
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National Minority AIDS Council
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